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14. ABSTRACT
Our highly innovative project is designed to identify more precise, performance-based measures of the Broader Autism Phenotype (BAP). In particular, we are focusing on the social communication difficulties commonly experienced by people with the BAP using sophisticated techniques that we developed to capture the acoustic properties of speech important for emotional expression. We are investigating this issue in detail in individuals with and without the BAP using a range of tasks measuring skills important in emotional and social interactions. This project also maps the brain systems that underpin social communication in the BAP by using state-of-the-art brain imaging techniques that measure brain structure and function. We aim to link these behavioural and brain findings to gain a more complete understanding of the BAP.

In terms of our progress to date, we have fully developed and piloted our research protocols and trained our Research Assistant in all skills relevant to the study (as described under our initial Statement of Work). We spent an additional 6-months in piloting our protocols and training our Research Assistant to ensure that all protocols were working optimally to provide the most robust and cutting-edge scientific techniques. This was particularly relevant for the development of our novel neuroimaging protocol and an interactive, web-based computer program designed for efficient collection of behavioural data. Using the behavioural and neuroimaging protocols (Experiments 1 and 2), we are now in the data collection phase of the study and plan to recruit the remaining participants over the next 6 months, in accordance with our Statement of Work. The increased time period required to develop our neuroimaging and behavioural protocols means that we require a 6-month extension for the final report of the study (initial deadline: July19, 2014; proposed extended deadline: Jan 19, 2015).

15. SUBJECT TERMS
Broader Autism Phenotype (BAP), Autism Spectrum Disorder (ASD), Social Communication, Vocal Emotion Processing, Functional Magnetic Resonance Imaging (fMRI), Structural MRI

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INTRODUCTION

Our highly innovative project is designed to identify more precise, performance-based measures of the Broader Autism Phenotype (BAP). In particular, we are focusing on the social communication difficulties commonly experienced by people with the BAP using sophisticated techniques that we have developed to capture the acoustic properties of speech important for emotional expression. We are investigating this issue in detail in individuals with and without the BAP using a range of tasks measuring skills important in emotional and social interactions. This project also maps the brain systems that underpin social communication in the BAP by using state-of-the-art brain imaging techniques that measure brain structure and function. We aim to link these behavioural and brain findings to gain a more complete understanding of the BAP.

We have chosen to assess people from rare large families in which there are many members with either autism or the BAP with these social communication difficulties. This will allow us to trace complex genetic patterns in these families, so that we may assess how the social-relatedness difficulties associated with autism and the BAP are inherited across generations. This is an effective way to find dominant genes causing social difficulties in autism and the BAP. In this way, the current project not only changes how autistic traits are viewed; as falling along a spectrum that blends with the normal population. It also gives neuroscientists insight into the changes in the brain that underpin autistic behaviour. This project therefore lays the vital foundations for the development of targeted treatments specifically designed to ease the profound social difficulties than can be experienced by people with autism spectrum disorders.

BODY

The information below describes the research accomplishments associated with each key task or milestone outlined in the approved Statement of Work. Please note that the effective start date for this Statement of Work was **April 19, 2013**.

Task 1: Development of research protocol *(April 19, 2013 – July 19, 2013)*

Milestone #1: Regulatory review and approval for human study

Local IRB (Royal Children's Hospital, Human Research Ethics Committee) approval to conduct the study was granted on July 23, 2012. Reports for annual continuing review were subsequently submitted and approved by our local IRB on December 12, 2012 and November 11, 2013. All relevant IRB-related documents have been sent to the HRPO Officer assigned to our study, as requested.

1.a Pilot the behavioural and neuroimaging paradigms (April 19, 2013 – January 19, 2014)

Behavioural Paradigm (Experiment 1): An interactive web-based computer program has been purpose-built and extensively piloted to collect data for the specific tasks included in the behavioural paradigm. Among other things, this web-based program incorporates a range of vocal sound files of varying nonverbal emotions to which participants respond. It also uses highly innovative purpose-built voice recording software to collect participant samples of emotions. Additional time was required to fully develop this highly innovative software, which is the first of its kind in the field. This extended the task development time frame by 6 months to ensure optimal functioning of the web-based software, minimal data loss over the long-term, and maximal efficiency of data collection processes. The program is now fully operational and successful piloting of participants is complete.

Neuroimaging Paradigm (Experiment 2): An in-scanner set of tasks that produce behavioural responses equivalent to the out-of-scanner behavioural paradigm has also been purpose-developed and extensively piloted. This will ensure that patterns of brain activation collected in-scanner can be accurately correlated with out-of-scanner behavioural performance to ensure cognitive and emotional processes of interest are effectively captured. The neuroimaging paradigm was developed over the same time frame as the behavioural paradigm described above, again to provide the most robust and cutting-edge scientific techniques for use in-scanner and to ensure that we have developed the best protocol for identifying functional activity associated with our key research questions. The paradigm also employs state-of-the-art structural MRI techniques, for which our research team is recognised as leading the field. The neuroimaging paradigm is now fully operational and piloting of participants is complete. Combined, the behavioural and neuroimaging paradigms represent sophisticated research tools that will underscore the success of the project.

1.b Train the Research Assistant in all procedural aspects of the daily running of the study to ensure efficient recruitment, and data collection, coding, and entry.

The Research Assistant has been fully trained and is now highly competent in all procedural aspects of the daily running of the study. She is currently engaged in participant recruitment, data coding and entry. She will continue to receive supervision and support from Principal Investigator, Wilson, throughout the duration of the study.

Task 2: Protocol and technique ***(January 19, 2014 – April 19, 2014)***

Milestone #2: Recruit 80 individuals with the BAP from rare large families with at least 10 affected members, as well as 40 age-, sex-, and IQ-matched controls

2.a Assess all family members with the Family History Interview and cognitive and behavioural measures to determine BAP status

This aspect of the study has been successfully completed for 50 of the 80 participants to date. We expect to recruit the remaining participants over the coming 3 months.

2.b Analyse social discourse of family members using purpose-written auditory software in MATLAB (R2009) to identify individuals with and without the psychoacoustic marker (BAP+P and BAP-P)

This aspect of the study has been successfully completed for 50 of the 80 participants. We expect to recruit the remaining participants over the coming 3 months.

2.c Identify matched controls, including screening for the presence of the psychoacoustic marker and a history of neurological, psychiatric or hearing disorders.

This aspect of the study has been successfully completed for 13 of the 40 participants. We expect to recruit the remaining participants over the coming 3 months.

Task 3: Participant ascertainment ***(January 19, 2014 – July 19, 2014)***

Milestone #3: Conduct Experiment 1 to behaviourally delineate the psychoacoustic endophenotype and link it to broader measures of pragmatic language, empathy and social cognition

3.a Collect behavioural data using the MAV task, the Goldman-Eisler Cartoon Task and the Interpersonal Reactivity Index in 120 participants.

This aspect of the study has been successfully completed for 13 participants to date. We expect to recruit the remaining participants over the coming 6 months.

3.b Analyse behavioural data using IB SPSS Statistics (Version 19.0). Prepare presentations and manuscripts to publish the research findings.

Preparation of the data for analysis using IB SPSS Statistics has commenced, including processing of sound files and coding of all participant responses collected to date. Plans are underway to prepare the initial findings of the study for presentation at national and international conferences over the coming 12 months.

Task 4. Publication of behavioural findings and presentation of results at international conference

Milestone #4: Conduct Experiment 2 to delineate the BAP+P neural endophenotype using functional neuroimaging and voxel-based morphometry (VBM)

4.a Collect fMRI data using the in-scanner MAV task (January 19, 2014 – July 19, 2014)

Following successful piloting of the fMRI paradigm described above, participants are scheduled to undergo scanning over the coming 6 months.

4.b Collect structural MRI data using VBM (January 19, 2014 – July 19, 2014)

Following successful piloting of the structural imaging paradigm described above, participants are scheduled to undergo scanning over the coming 6 months.

4.c Analyse the neuroimaging data to identify neural endophenotypes and link these to the behavioural data to examine the relationship between the neural and psychoacoustic endophenotypes, and their sensitivity and specificity to the BAP. Prepare presentations and manuscripts to publish the research findings. (July 19, 2014 – October 19, 2014)

Pilot data collected to date are currently being analysed, with the final behavioural and neuroimaging analyses aimed to be completed within the coming 9 months.

Task 5: Publication of structural and functional neuroimaging results and presentation of results at international conferences *(July 19, 2014 – October 19, 2014)*

Plans are underway to prepare the initial findings of the study for presentation at national and international conferences over the coming 12 months.

KEY RESEARCH ACCOMPLISHMENTS

The information below summarises the key research accomplishments to date:

- IRB approval of study and successful ongoing IRB review of study across 2012-2014.
- Development of the behavioural and neuroimaging paradigms (Experiments 1 and 2), which includes designing an interactive web-based computer program and programming functional and structural MRI scans.
- Ongoing training of the Research Assistant in paradigm development, data collection and data analysis for Experiments 1 and 2.
- Systematic development and pilot testing of participants to develop a novel interactive web-based computer program for the collection of behavioural data from Experiment 1.
- Systematic development and pilot testing of a highly sophisticated neuroimaging paradigm.
- Development of auditory software for analysis of voice recordings of BAP and control participants.
- Characterisation of the Broader Autism Phenotype (BAP) in family members of large families with multiple individuals affected with Autism Spectrum Disorder (ASD).
- Recruitment of control participants for participation in the study.
- Ongoing data collection for Experiment 1.
- Experimental design and proposed data analyses presented at three scientific research meetings in 2013.
- Plans to analyse the initial data for presentation at relevant scientific conferences and meetings.

REPORTABLE OUTCOMES

The scope, rationale, proposed experimental design and proposed data analyses were presented at three scientific research meetings in 2013, as follows:

1) *Verbal Pragmatics and Vocal Emotion Processing in the Broader Autism Phenotype.* Oral presentation, Neurocognition & Neuroimaging Laboratory, The University of Melbourne, March, 2013.

2) *Verbal Pragmatics and Vocal Emotion Processing in the Broader Autism Phenotype.* Oral presentation, Collaborative Autism Team Study, Annual Autism Retreat, The University of Melbourne. This retreat is well attended by researchers from The University of Melbourne, the Royal Children's Hospital, the Melbourne Brain Centre, and the Florey Institute of Neuroscience and Mental Health, May, 2013.

3) *Verbal Pragmatics and Vocal Emotion Processing in the Broader Autism Phenotype.* Platform presentation, Neurocognition & Neuroimaging Workshop, 2013 Epilepsy Research Retreat, Melbourne Brain Centre, Florey Institute of Neuroscience & Mental Health, The University of Melbourne, Australia, July 2013.

CONCLUSION

To date, the work completed on this project, corresponding to the approved Statement of Work, indicates that the study is progressing well. Additional time has been spent on developing a novel and innovative interactive web-based computer program (for Experiment 1) and a cutting-edge neuroimaging protocol (for Experiment 2) to maximize the success and impact of the study. These behavioural and neuroimaging protocols represent significant advancements on existing approaches in the field and will yield exciting findings once data collection is complete. Data collected thus far have been obtained in accordance with human ethics regulations established by the local IRBs associated with the study, and preliminary findings are consistent with our expectations.